

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
30 November 2000 (30.11.2000)

PCT

(10) International Publication Number
WO 00/71116 A1

(51) International Patent Classification⁷: **A61K 31/40,**
C07D 207/34

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(21) International Application Number: **PCT/IB00/00014**

(22) International Filing Date: **6 January 2000 (06.01.2000)**

(25) Filing Language: **English**

(26) Publication Language: **English**

(30) Priority Data:
775/DEL/99 **25 May 1999 (25.05.1999)** **IN**

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(81) Designated States (*national*): AE, AL, AM, AT, AU, AZ,
BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK,
DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,
IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT,
RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,
UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent
(AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent
(AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU,
MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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WO 00/71116 A1

(54) Title: **PROCESS FOR THE PRODUCTION OF AMORPHOUS ATORVASTATIN CALCIUM**

(57) Abstract: A process for the preparation of amorphous atorvastatin calcium and hydrates thereof which comprises: (a) dissolving crystalline atorvastatin calcium in a non-hydroxylic solvent; (b) adding a non-polar hydrocarbon anti-solvent or adding the dissolved atorvastatin to the non-polar anti-solvent to precipitate out atorvastatin calcium; and (c) removing the solvent by filtration to afford amorphous atorvastatin calcium.

EXPRESS MAIL NO. EV545395338US
DOCKET NO. PC25264A

**PROCESS FOR THE PRODUCTION OF
AMORPHOUS ATORVASTATIN CALCIUM**

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FIELD OF THE INVENTION

The present invention relates to a process for the production of amorphous atorvastatin calcium.

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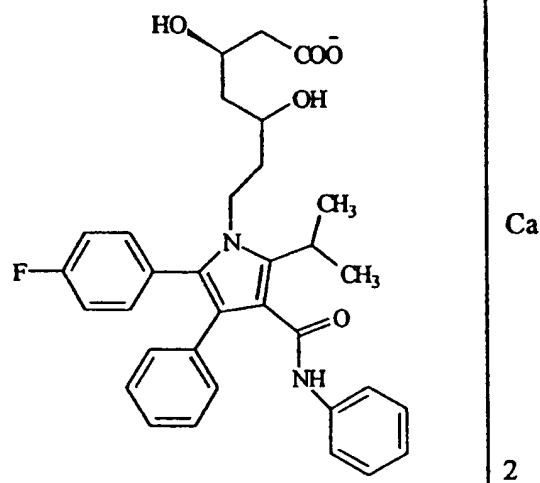
BACKGROUND OF THE INVENTION

Atorvastatin is chemically [R-(R*,R*)]-2-(4-fluoro-phenyl)- β dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H pyrrole-1-heptanoic acid. Atorvastatin calcium, a synthetic HMG-CoA reductase inhibitor, is used for the treatment of hyperlipidemia and hypercholesterolemia, both of which are risk factors for arteriosclerosis and coronary heart disease. Open dihydroxy carboxylic acid, lactone and various salt forms of atorvastatin have been synthesized.

15

United States Patent 5,273,995, describes that R-form of the ring opened acid form has surprising inhibition of the biosynthesis of cholesterol. Atorvastatin in its calcium salt form, i.e. [R-(R*,R*)]-2-(4-fluoro-phenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1) having Formula 1:

20



10 is more suited to formulations and has been recommended as a drug.

United States patents 5,003,080; 5,097,045; 5,103,024; 5,124,482; 5,149,837; 5,248,793; 5,280,126; 5,342,952, which are herein incorporated by reference, describe
15 various processes and key intermediates for preparing atorvastatin.

Atorvastatin calcium produced by the processes described in the above mentioned United States patents does not give amorphous atorvastatin consistently but gives a mixture of its crystalline and amorphous forms, which has unsuitable filtration and drying characteristics and are not suitable for large-scale production.

20 PCT application, WO 97/03959, discloses novel crystalline forms of atorvastatin calcium designated as Form I, Form II, and Form IV and method for their preparation which provide more favourable filtration and drying characteristics.

PCT application WO 97/03960 describes a procedure for converting the crystalline form of atorvastatin to the amorphous form. Process disclosed therein comprises dissolving crystalline form-I atorvastatin in a non-hydroxylic solvent like tetrahydrofuran or mixtures of tetrahydrofuran and toluene. The process involves
5 complete removal of the solvent under high temperature (about 90°C) and high vacuum (about 5mm) using capital intensive equipment. Exposure of the material to high temperature for several days leads to degradation of the product. This makes the process very inconvenient to operate at a large scale. Slow removal of solvents at a manufacturing scale renders this process as inefficient cost-wise and less productive.

10

SUMMARY OF THE INVENTION

It is an objective of the present invention to provide an efficient process for the production of amorphous atorvastatin, which eliminates the problems of prior art and is convenient to operate on a commercial scale.

15

Accordingly, the present invention provides a process for the preparation of atorvastatin calcium in an amorphous form which comprises dissolving crystalline atorvastatin in a non-hydroxylic solvent, adding a suitable non-polar hydro-carbon solvent and recovering atorvastatin from a solution thereof, by solvent precipitation, isolating and drying the product.

20

Generally, the product can be isolated by any standard method known in the art such as by filtration, centrifugation or decantation. Typically, this product is isolated by filtration when any of the solvents within the scope of the process are used.

Major advantages of the present invention compared to the prior art processes are:

- i. elimination of the need to remove solvent by drying techniques.
- ii. less time consuming with improved filtration.
- 5 iii. easy to operate on large-scale.
- iv. reproducibly produces amorphous product having allowable levels of residual solvents.

The present invention thus provides a novel process for the preparation of amorphous atorvastatin calcium and hydrates thereof which comprises:

- 10 (a) dissolving crystalline atorvastatin calcium in a non-hydroxylic solvent;
- (b) adding a non-polar hydrocarbon anti-solvent to precipitate out the material; and
- (c) removing the solvent by filtration to afford amorphous atorvastatin calcium

15 The non-hydroxylic solvent is selected from a group of solvents, which have the ability to dissolve crystalline atorvastatin and includes tetrahydrofuran. Suitable non-polar hydrocarbon solvents are selected from a group consisting of: n-hexane, n-heptane, cyclohexane, hexane fraction, heptane fraction or the like. In a preferred embodiment of this invention, the non-hydroxylic solvent is tetrahydrofuran and anti-
20 solvent is n-hexane, cyclohexane or n-heptane.

Generally, crystalline atorvastatin calcium is dissolved in a non-hydroxylic solvent, e.g. tetrahydrofuran, at a concentration of about 15% w/v to about 40% w/v, preferably at a concentration of about 25% w/v to about 15% w/v at ambient

temperature and a non-polar hydrocarbon, preferably n-hexane, cyclohexane or n-heptane, is added at 0°C to 50°C, preferably at 20°C to 25°C. The product is recovered by filtration at ambient temperature. Filtration, which is fast and smooth, is carried out using nutsche filtration or centrifuge filtration. Preferably, nutsche
5 filtration is used on large scale preparation. Filtered material, a semi-dry powder, is further dried to remove surface solvents in a vacuum tray drier, tray drier, fluid bed drier or a rotary vacuum drier to afford amorphous material. Preferably, material is dried in a vacuum tray drier at about 20°C to about 80°C for 6 hours to 24 hours. Most preferably, drying is carried out at about 50°C to about 60°C for 12 hours.

10 Quantity of antisolvent varies from 5 times to 50 times the input of crystalline atorvastatin calcium depending upon its solution in non-hydroxylic solvent. Preferably, the quantity of antisolvent used is about 20 times to about 40 times the input of crystalline atorvastatin calcium to make overall concentration of about 5% w/v to about 2.5 w/v%.

15 Amorphous atorvastatin calcium prepared according to the process of the present invention may be characterized by its x-ray powder diffraction pattern (Figures 2) as shown in the accompanied drawings. X-ray powder diffraction patterns (Figures 2) show no peaks which are characteristic of a crystalline atorvastatin calcium (Figure 1 of the accompanied drawings) thus demonstrating the amorphous nature of the
20 product.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is the diffractogram of crystalline atorvastatin calcium. The horizontal axis represents 2θ and the vertical axis corresponds to peak intensity.

Figure 2 is diffractogram of amorphous atorvastatin calcium. The horizontal axis represents 2θ and the vertical axis corresponds to peak intensity.

The present invention is illustrated by the following examples, which are not intended to limit the effective scope of the claims.

DETAILED DESCRIPTION OF THE INVENTION

Example 1

[R-(R*,R*)-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-
[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemicalcium salt
(Amorphous Atorvastatin calcium).

Method A

Crystalline atorvastatin calcium (10 kg) was dissolved in tetrahydrofuran (30 lt) under stirring at ambient temperature. Clear solution so obtained was added slowly to cyclohexane (350 lt) under nitrogen atmosphere. It was vigorously stirred maintaining temperature at 20-25°C. The precipitated product was centrifuged and dried under vacuum at about 60°C for 12 hours. Atorvastatin (9.5 kg) in an

amorphous form was obtained having residual solvent levels of 0.01% w/w tetrahydrofuran and 0.6% w/w cyclohexane. X-ray powder diffraction pattern (Figure 2 as shown in the accompanied drawings) demonstrate the amorphous nature of the product.

5

Method B

Crystalline atorvastatin calcium (10 kg) was dissolved in tetrahydrofuran (30 lt) under stirring at ambient temperature. To a clear solution of atorvastatin, cyclohexane (350 lt) was added under vigorous stirring at 20 to 25°C. The precipitated mass was further stirred for 30 minutes and filtered in a centrifuge. The product was dried under vacuum at about 60°C for 12 hours. Atorvastatin (9.6 kg) in an amorphous form was obtained having residual solvent levels of 0.01% w/w for tetrahydrofuran and 0.7% w/w for cyclohexane. X-ray powder diffraction pattern demonstrates the amorphous nature of the product.

15

Example 2

[R-(R*,R*)-2-(4-fluorophenyl)β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-
[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemicalcium salt
(Amorphous Atorvasatin calcium)]

20

The process of Example 1 was repeated with crystalline atorvastatin calcium (10 kg) dissolved in tetrahydrofuran (30 lt) and using n-hexane instead of cyclohexane

to give amorphous atorvastatin (9.5 kg.). X-ray crystallography confirmed the amorphous nature of the product.

Example 3

5 **[R-(R*,R*)]-2-4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-
[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemicalcium salt
(Amorphous Atorvasatin calcium)**

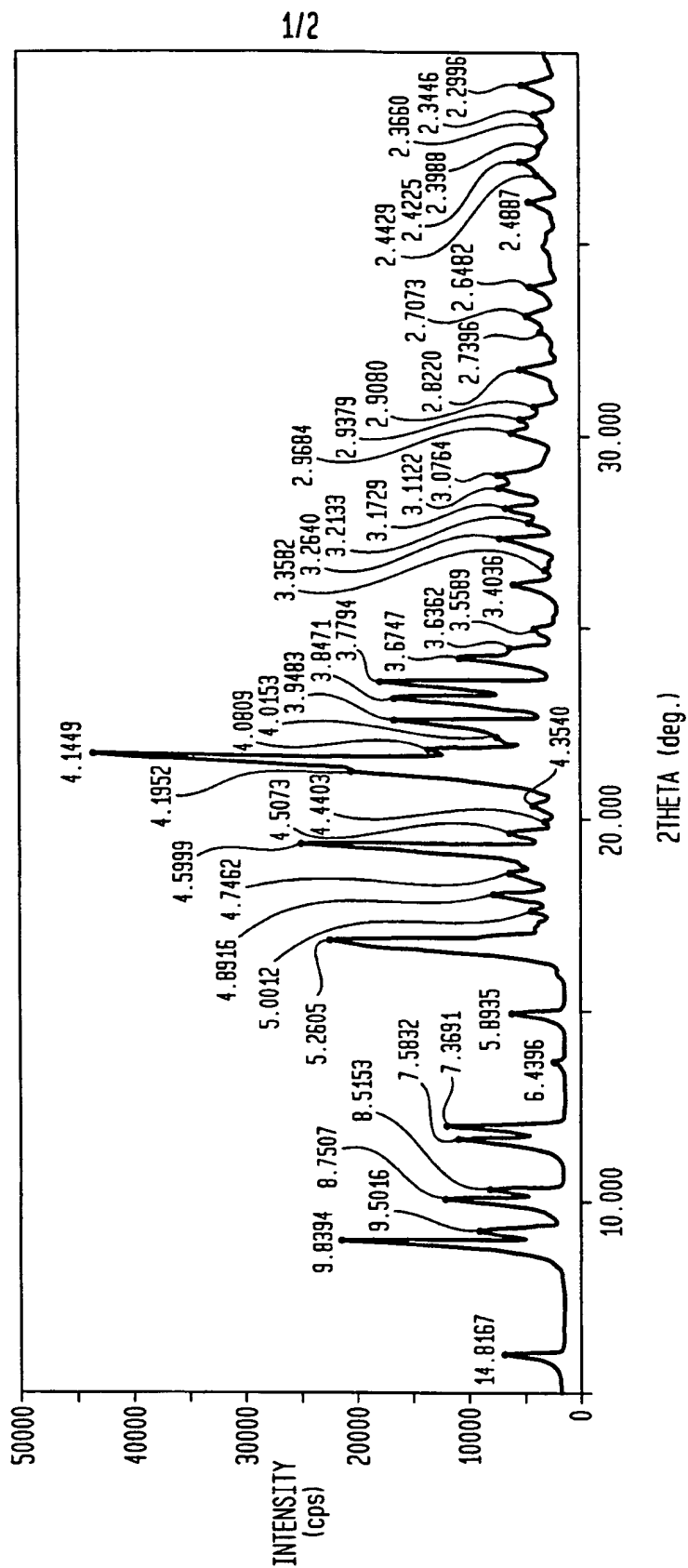
The process of Example 1 was repeated with crystalline atorvastatin calcium (10 kg)
10 dissolved in tetrahydrofuran (30 lt) and using n-heptane instead of cyclohexane to
give amorphous atorvastatin (9.6 kg). X-ray crystallography examination confirmed
the amorphous nature of the product.

While the present invention has been described in terms of its specific
embodiments, certain modifications and equivalents will be apparent to those skilled
15 in the art and are intended to be included within the scope of the present invention.

WE CLAIM:

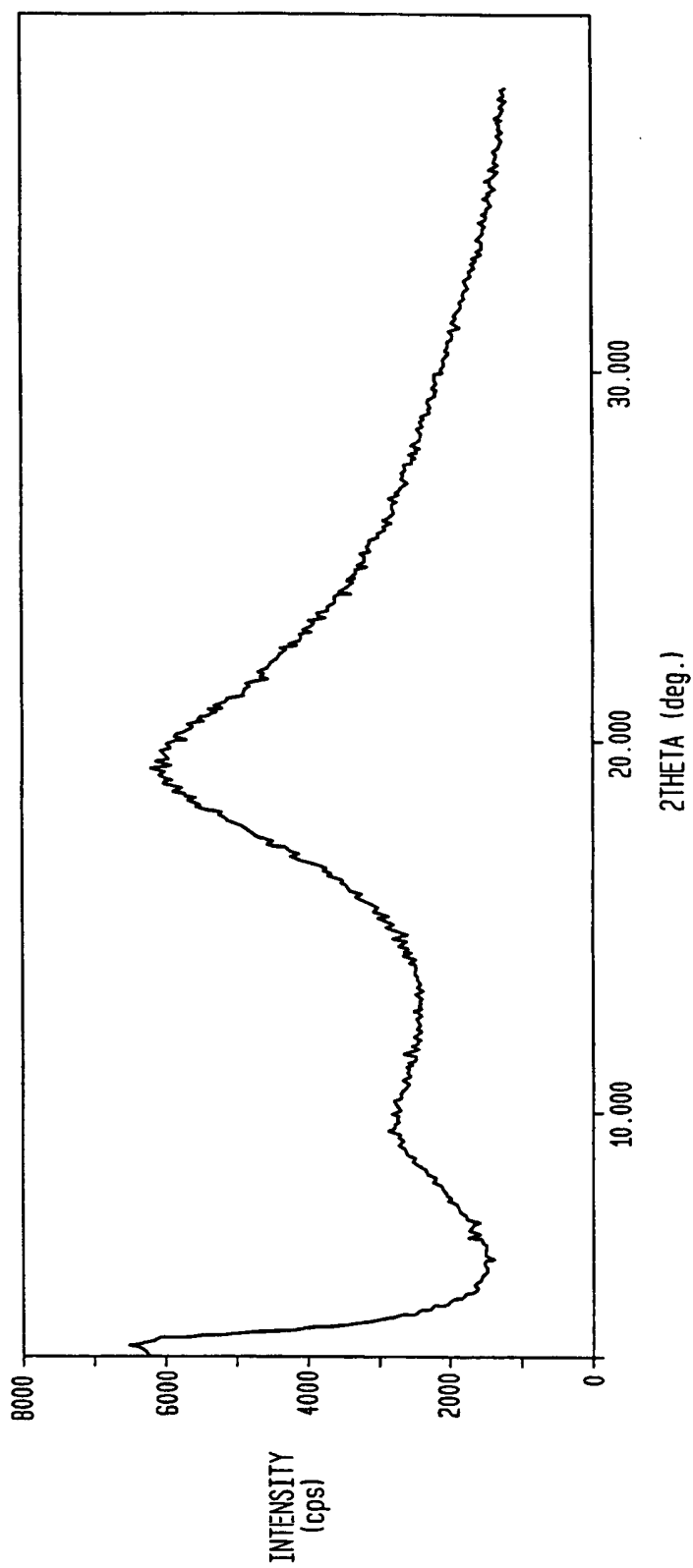
1. A process for the preparation of amorphous atorvastatin calcium and hydrates thereof which comprises:
 - (a) dissolving crystalline atorvastatin calcium in a non-hydroxylic solvent;
 - (b) adding a non-polar hydrocarbon anti-solvent or adding the dissolved atorvastatin to the non-polar anti-solvent to precipitate out atorvastatin calcium; and
 - (c) removing the solvent by filtration to afford amorphous atorvastatin calcium.
2. The process of claim 1, wherein the non-hydroxylic solvent is tetrahydrofuran and anti-solvent is chosen from a group of non-polar hydrocarbon solvents comprising n-hexane, cyclohexane or n-heptane.
3. The process of claim 1, wherein the non-hydroxylic solvent is tetrahydrofuran and anti-solvent is n-hexane.
4. The process of claim 1, wherein the non-hydroxylic solvent is tetrahydrofuran and anti-solvent is cyclohexane.
5. The process of claim 1, wherein the non-hydroxylic solvent is tetrahydrofuran and anti-solvent is n-heptane.
6. The process of claim 1, wherein said amorphous atorvastatin calcium is isolated by filtration.

FIG. 1



2/2

FIG. 2



INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 00/00014

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K31/40 C07D207/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 03959 A (WARNER LAMBERT CO ;BRIGGS CHRISTOPHER A (US); JENNINGS REX ALLEN () 6 February 1997 (1997-02-06) cited in the application	1-6
A	DE 33 27 449 A (GLAXO GROUP LTD) 2 February 1984 (1984-02-02) page 9, line 7 - line 16 page 12, line 10 -page 13, line 12	1-6
A	WO 97 03960 A (WARNER LAMBERT CO ;LIN MIN (US); SCHWEISS DIETER (US)) 6 February 1997 (1997-02-06) cited in the application claim 1	1-6
	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

10 May 2000

Date of mailing of the international search report

17/05/2000

Name and mailing address of the ISA
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INTERNATIONAL SEARCH REPORT

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PCT/IB 00/00014

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 03958 A (WARNER LAMBERT CO ;MCKENZIE ANN T (US)) 6 February 1997 (1997-02-06) cited in the application <u> </u>	1-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 00/00014

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9703959 A	06-02-1997	AU 6484296 A	18-02-1997
		BG 102187 A	30-10-1998
		BR 9609872 A	23-03-1999
		CA 2220018 A	06-02-1997
		CN 1190955 A	19-08-1998
		CZ 9800121 A	14-10-1998
		EP 0848705 A	24-06-1998
		HR 960339 A	30-04-1998
		HU 9900678 A	28-07-1999
		IL 122118 A	14-07-1999
		JP 11509230 T	17-08-1999
		NO 980207 A	16-01-1998
		PL 324496 A	25-05-1998
		SK 6298 A	07-10-1998
		US 5969156 A	19-10-1999
DE 3327449 A	02-02-1984	AT 382154 B	26-01-1987
		AT 276783 A	15-06-1986
		AU 566881 B	05-11-1987
		AU 1741783 A	02-02-1984
		BE 897422 A	30-01-1984
		CA 1240313 A	09-08-1988
		CH 657134 A	15-08-1986
		CZ 280528 B	14-02-1996
		CS 8305687 A	15-03-1988
		CY 1434 A	02-09-1988
		DE 3374010 D	12-11-1987
		DK 68392 A	25-05-1992
		DK 349083 A, B,	31-01-1984
		EP 0107276 A	02-05-1984
		ES 524590 D	01-06-1985
		ES 8505689 A	01-10-1985
		FI 832757 A, B,	31-01-1984
		FR 2531087 A	03-02-1984
		GB 2127401 A, B	11-04-1984
		GR 79349 A	22-10-1984
		HK 84288 A	28-10-1988
		HU 190603 B	29-09-1986
		IE 55748 B	02-01-1991
		IL 69375 A	31-12-1986
		IT 1168206 B	20-05-1987
		JP 2025666 C	26-02-1996
		JP 7030084 B	05-04-1995
		JP 59044391 A	12-03-1984
		KE 3805 A	03-06-1988
		KR 9100046 B	19-01-1991
		LU 84935 A	23-11-1983
		MY 5887 A	31-12-1987
		NL 8302705 A	16-02-1984
		NO 832773 A, B,	31-01-1984
		NZ 205083 A	14-03-1986
		PL 243228 A	27-08-1984
		PT 77135 A, B	01-08-1983
		SE 453195 B	18-01-1988
		SE 8304208 A	31-01-1984
		SG 26088 G	15-07-1988
		SI 8311558 A	31-12-1995
		SK 403191 A	11-07-1995

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 00/00014

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 3327449 A		SU 1266471 A	23-10-1986
		US 4994567 A	19-02-1991
		US 5013833 A	07-05-1991
		US 4562181 A	31-12-1985
		US 4820833 A	11-04-1989
		YU 155883 A	30-04-1986
		ZA 8305579 A	26-09-1984
		ZW 17383 A	26-10-1983
WO 9703960 A	06-02-1997	AU 700794 B	14-01-1999
		AU 6497896 A	18-02-1997
		BG 102188 A	31-08-1998
		BR 9609714 A	23-02-1999
		CA 2220455 A	06-02-1997
		CN 1190956 A	19-08-1998
		CZ 9800122 A	16-12-1998
		EP 0839132 A	06-05-1998
		HR 960312 A	28-02-1998
		IL 122161 A	14-07-1999
		JP 11510486 T	14-09-1999
		NO 980209 A	16-01-1998
		PL 324463 A	25-05-1998
		SK 5898 A	05-08-1998
WO 9703958 A	06-02-1997	AU 6484196 A	18-02-1997
		BG 102186 A	30-10-1998
		BR 9610567 A	06-07-1999
		CA 2220458 A	06-02-1997
		CN 1190957 A	19-08-1998
		CZ 9800123 A	17-06-1998
		EP 0848704 A	24-06-1998
		HR 960313 A	30-04-1998
		HU 9901687 A	28-10-1999
		IL 122162 A	14-07-1999
		JP 11509229 T	17-08-1999
		NO 980208 A	16-01-1998
		PL 324532 A	08-06-1998
		SK 5998 A	06-05-1998